REMARKS / ARGUMENTS

Reconsideration of the above-identified application in view of the amendments above and the following remarks is respectfully requested.

Claims 1 through 93 remain in this application. Claims 1, 5, 6, 9, 10, 13, 14, 16, 17, 19, 20, 22-28, 30, 38, 39, 44, 47, 50, 51, 54, 55, 58, 59, 61, 62, 64, 65, 67-72, 75, 76, 84, 85, 90 and 93 have been amended.

§ 112 First Paragraph Rejections

The Examiner has rejected Claims 3, 12, 15, 18, 48, 56, 57, 60 and 63 under the first paragraph of § 112 as containing subject matter not described in the specification in such a way as to enable one skilled in the art to use the invention. Specifically, the Examiner requests to see evidence of the antifungal, antibacterial, antiviral, antipsoriatic activity of the agents listed in the claims in the present compositions when combined with hydrophobic water-insoluble polymer derivative.

Applicant wishes to respectfully bring to the attention of the Examiner that as explained hereinbelow in greater detail, once applied, the agents are not necessarily active when trapped within the polymer derivative but rather are confined in a substantially aqueous solution trapped underneath the layer produced by the polymer of the composition (see page 6 line 19 to page 7 line 5, page 18 line 15 to page 19 line 6). The effectivity of the agents of Claims 3, 12, 15, 18, 48, 56, 57, 60 and 63 in an aqueous solution is well documented.

§ 112 Second Paragraph Rejections

The Examiner has rejected Claims 1, 28, 47 and 93 under the second paragraph of § 112 as being indefinite. The language of these Claims has been modified, without prejudice, in order to clarify the intent of Applicant

The Examiner has also requested that the language of Claims 1, 5, 6, 9, 10, 13, 14, 16, 17, 19, 20, 22-25, 30, 38, 39, 44, 50, 51, 54, 55, 58, 59, 61, 62, 64, 65, 67-70, 75, 76, 84, 85 and 90 as well as of Claims 26, 27, 71 and 72 be modified. The language of these Claims has been modified, without prejudice, in line with the suggestions of the Examiner.

§ 103 Rejections – Friedman et al (5,160,737) in view of Nimni (5,487,776) and also in view of Hutchins et al. (5,863,527)

The Examiner has rejected Claims 1-6, 9-17, 21, 26, 27, 29-31, 33, 34, 36-39, 41, 42, 46, 92 and 93 under § 103 as being unpatentable over Friedman et al (US 5,160,737) in view of Nimni (US 5,487,776). The Examiner has also rejected Claims 1-14, 16-28, 30, 31-45, 47-91 and 93 as being unpatentable over Friedman et al (US 5,160,737) in view of Hutchins et al. (US 5,487,776). The Examiner's rejections are respectfully traversed.

Friedman relates to a polymer composition that is useful in producing a therapeutic or prophylactic layer configured to continuously release a medically useful agent (hereinfurther therapeutic agent). The composition has two purposes. First, the composition solidifies through polymerization or evaporation of therein contained solvents to produce a film, which effectively adheres to a surface such as skin or tooth enamel (column 12 lines 5-10). Second, the polymer decomposes *in situ*

releasing the therapeutic agent into the surrounding milieu (column 12 lines 63-66). Thus the composition taught by Friedman is a classic sustained release delivery system. To emphasize this, it is seen that the composition necessarily contains a release-adjusting agent (column 11 lines 31-34, column 12 lines 34-37) to maintain a clinically effective concentration of the therapeutic agent in the treated area. The therapeutic agent is contained within the polymer matrix and it is the action of the release-adjusting agent that makes the composition useful by controlling the rate of polymer decomposition and thus the rate with which the therapeutic agent escapes the polymer. Once the agent escapes into an aqueous solution such as found in the mouth or skin, the therapeutic agent is active. Friedman also teaches adding a humectant to the composition to allow for even further polymer decomposition rate control (column 16 lines 25-27).

The present invention teaches of a composition useful in delivering a therapeutic agent to a surface such as a nail. Once applied, the composition forms a water-impermeable layer on top of the nail. The layer traps a layer of water (and optionally a keratolytic agent) in contact with the nail. Due to the solubility of the therapeutic agent in the water, some therapeutic agent applied is trapped in an aqueous solution in immediate proximity of and in contact with the nail. A significant amount of humectant is added in order to increase the amount of water trapped under the layer and in contact with the nail. The presence of the relatively large amount of water in contact with the nail acts to increase the permeability of the nail, allowing the therapeutic agent to penetrate into the nail to effect a significant increase in therapeutic efficacy of the therapeutic agent. The addition of a keratolytic agent, concentrated in proximity of the nail by the presence of the water, acts to

further increase the permeability of the nail, increasing the efficacy of the therapeutic agent even further. It is important to note that there are likely therapeutic agent molecules confined within the polymer and in contact with the trapped water layer. These confined molecules eventually leach out of the polymer and into the aqueous layer. This leaching out does not occur as a result of polymer decomposition.

Careful comparison of the teachings of Friedman and of the present invention show that the teachings of Friedman in no way apply to and in all cases teach away from the present invention:

i. Friedman teaches of the gradual release of a therapeutic agent into the surrounding milieu whereas the present invention concentrates an amount of an applied therapeutic agent in proximity of the applied surface; not in claims

ii. Friedman teaches of a polymer layer that necessarily disintegrates, whereas the present invention teaches of a polymer layer that acts as a shield to concentrate the therapeutic agent, the water and in some cases a keratolytic agent in proximity of the applied surface;

iii. Friedman teaches delivery of a therapeutic agent using a classic sustained-release mechanism whereas the present invention teaches a mechanism whereby a given amount of therapeutic agent has a prolonged effect.

The Examiner has also cited the teachings of Nimni in relation to the teachings of the present invention. Nimni teaches of a polymer composition containing the mycotoxic griseofulvin that when applied to a nail gradually forms a griseofulvin-containing water permeable layer (column 3 line 51). The griseofulvin gradually leaches out of the layer (column 4 line 64). Just as Friedman, Nimni teaches a classic sustained release therapeutic agent delivery mechanism. Nimni does

not teach the addition of water to the composition but rather exclusively organic solvents (column 3 line 45-48). Nimni does not teach of adding a humectant to a composition, which would conceivably draw water from the surrounding milieu and concentrate it in the area of a nail. Thus Nimni teaches away from and in no way considers the problem solved by the present invention.

The Examiner has also cited the teachings of Hutchins in relation to the teachings of the present invention, specifically as concerns the presence of a keratolytic agent in a composition. Hutchins teaches the use if a keratolytic agent as an active agent, that is for the anti-acne properties of a keratolytic agent (column 19 lines 25-30). Hutchins does not teach the use of a keratolytic agent in increasing the permeability of the nail, increasing the efficacy of a therapeutic agent as taught in the present invention.

While continuing to traverse the Examiner's rejections, the Applicant has, in order to expedite the prosecution, chosen to amend the preamble of independent Claims 1, 47 and 93 in order to clarify and emphasize the difference between the innovative mechanism of action of the present invention and of Friedman. Specifically, Claims 1, 47 and 93 have been amended by replacing "*sustained release nail varnish*" with "*prolonged effect therapeutic nail varnish*".

Further, in order to emphasize the difference between the film of the present invention and the prior art, Claims 1 and 47 have been amended by the addition of the text "*said film-forming agents being selected so as to form a film upon evaporation of said volatile solvent, said film configured to trap water in contact with a nail.*" Claim 93 has been amended by the addition of the text "*said film-forming agents being selected so as to form a film upon evaporation of said*

volatile solvent, said film configured to trap water in contact with the nail and the surrounding tissues."

Amended independent Claims 1, 47 and 93 now feature language that makes it absolutely clear that prior art cited by the Examiner teaches away from the present invention. Applicant believes that the above arguments completely overcome the Examiner's rejections on § 103 grounds.

Attached hereto is a marked-up version of the changes made to the Claims. The attached page is captioned "**Version with markings to show changes made.**"

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully Submitted,

Mark M. Friedman
Attorney for Applicant
Registration No. 33,883

29 August, 2001

Version with markings to show changes made

1. A ~~sustained release~~ **prolonged effect therapeutic** nail varnish composition comprising:

(a) a pharmaceutically effective agent;

(b) a humectant;

(c) water;

(d) less than about 7.5% ~~(w/w) based on~~ **of** the total weight of the composition, of a polymeric film-forming agent;

(e) at least one additional excipient; and

(f) a solvent system, ~~including~~ **said solvent system containing** at least one volatile solvent;

said film-forming agents being selected so as to form a film upon evaporation of said volatile solvent, said film configured to trap water in contact with a nail.

5. The nail varnish of claim 2, wherein said antifungal agent is present in an amount of less than about 1% ~~(w/w)~~ **of the**~~, relative to the~~ total weight of the composition.

6. The nail varnish of claim 2, wherein said antifungal agent is present in an amount of less than about 5% ~~(w/w) based on~~ **of** the **total** weight of the non-volatile components.

9. The nail varnish of claim 2, wherein said keratolytic agent is present in an amount of less than about 1%~~ (w/w) relative to the total~~ **of the total** weight of the composition.

10. The nail varnish of claim 2, wherein said keratolytic agent is present in an amount of from about 0.05% to about 5% ~~(w/w) based on~~ **of** the **total** weight of the non-volatile components.

13. The nail varnish of claim 11, wherein said antibacterial agent is present in an amount of from about 0.01% to about 1% ~~(w/w), relative to~~ **of** the total weight of the composition.

14. The nail varnish of claim 11, wherein said antibacterial agent is present in an amount of from about 0.05% to about 5% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

16. The nail varnish of claim 11, wherein said antiviral agent is present in an amount of from about 0.08% to about 0.8% ~~(w/w), relative to~~ **of** the total weight of the composition.

17. The nail varnish of claim 11, wherein said antiviral agent is present in an amount of from about 0.8% to about 8% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

19. The nail varnish of claim 11, wherein said antipsoriatic agent is present in an amount of from about 0.02% to about 2% ~~(w/w), relative to~~ **of** the total weight of the composition.

20. The nail varnish of claim 11, wherein said antipsoriatic agent is present in an amount of from about 0.1% to about 10% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

22. The nail varnish of claim 1, wherein said humectant is present in an amount of from about 3% to about 15% ~~(w/w), relative to~~ **of** the total weight of the composition.

23. The nail varnish of claim 1, wherein said humectant is present in an amount of from about 5% to about 35% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

24. The nail varnish of claim 1, wherein said water is present in an amount of less than about 5% ~~(w/w), relative to~~ **of** the total weight of the composition.

25. The nail varnish of claim 1, wherein said water is present in an amount of from about 0.4% to about 25% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

26. The nail varnish of claim 1, wherein said polymeric film-forming agent is selected from the group consisting of hydrophobic ~~(water insoluble)~~ polymers.

27. The nail varnish of claim 26, wherein said hydrophobic ~~(water insoluble)~~ polymer is selected from the group consisting of hydrophobic cellulose derivatives, hydrophobic methacrylic polymers, cellulose acetate phthalate, shellac, derivatives thereof, and mixtures thereof.

28. The nail varnish of claim 27, wherein said hydrophobic cellulose derivative**s are hydrophobic** ~~is selected from the group consisting of~~ ethyl cellulose ~~of any acceptable molecular weight~~ **derivatives**.

30. The nail varnish of claim 1, wherein said polymeric film-forming agent is present in an amount of from about 8% to about 35% **of** ~~(w/w), based on~~ the **total** weight of the non-volatile components.

38. The nail varnish of claim 36, wherein said plasticizer is present in an amount of from about 0.1% to about 2% ~~(w/w), relative to~~ **of** the total weight of the composition.

39. The nail varnish of claim 36, wherein said plasticizer is present in an amount of from about 0.5% to about 10% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

44. The nail varnish of claim 1, wherein said volatile solvent is present in an amount of from about 60% to about 90% ~~(w/w), relative to~~ **of** the total weight of the composition.

47. A ~~sustained release~~ **prolonged effect therapeutic** nail varnish composition comprising:

(a) an antifungal agent;

(b) a keratolytic agent;

(c) a humectant;

(d) water;

(e) a polymeric film-forming agent;

(f) at least one additional excipient; and

(g) a solvent system, ~~including~~ **said solvent system containing** at least one volatile solvent,

said film-forming agents being selected so as to form a film upon evaporation of said volatile solvent, said film configured to trap water in contact with a nail.

50. The nail varnish of claim 47, wherein said antifungal agent is present in an amount of less than about 1% ~~(w/w), relative to~~ **of** the total weight of the composition.

51. The nail varnish of claim 47, wherein said antifungal agent is present in an amount of less than about 5% ~~(w/w) based on~~ **of** the **total** weight of the non-volatile components.

54. The nail varnish of claim 47, wherein said keratolytic agent is present in an amount of less than about 1% ~~(w/w) relative to~~ **of** the total weight of the composition.

55. The nail varnish of claim 47, wherein said keratolytic agent is present in an amount of from about 0.05% to about 5% ~~(w/w) based on~~ **of** the **total** weight of the non-volatile components.

58. The nail varnish of claim 56, wherein said antibacterial agent is present in an amount of from about 0.01% to about 1% ~~(w/w), relative to~~ **of** the total weight of the composition.

59. The nail varnish of claim 56, wherein said antibacterial agent is present in an amount of from about 0.05% to about 5% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

61. The nail varnish of claim 56, wherein said antiviral agent is present in an amount of from about 0.08% to about 0.8% ~~(w/w), relative to~~ **of** the total weight of the composition.

62. The nail varnish of claim 56, wherein said antiviral agent is present in an amount of from about 0.8% to about 8% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

64. The nail varnish of claim 56, wherein said antipsoriatic agent is present in an amount of from about 0.02% to about 2% ~~(w/w), relative to~~ **of** the total weight of the composition.

65. The nail varnish of claim 56, wherein said antipsoriatic agent is present in an amount of from about 0.1% to about 10% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

67. The nail varnish of claim 47, wherein said humectant is present in an amount of from about 3% to about 15% ~~(w/w), relative to~~ **of** the total weight of the composition.

68. The nail varnish of claim 47, wherein said humectant is present in an amount of from about 5% to about 35% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

69. The nail varnish of claim 47, wherein said water is present in an amount of less than about 5% ~~(w/w), relative to~~ **of** the total weight of the composition.

70. The nail varnish of claim 47, wherein said water is present in an amount of from about 0.4% to about 25% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

71. The nail varnish of claim 47, wherein said polymeric film-forming agent is selected from the group consisting of hydrophobic ~~(water insoluble)~~ polymers.

72. The nail varnish of claim 71, wherein said hydrophobic ~~(water insoluble)~~ polymer is selected from the group consisting of hydrophobic cellulose derivatives, hydrophobic methacrylic polymers, cellulose acetate phthalate, shellac, derivatives thereof, and mixtures thereof.

75. The nail varnish of claim 47, wherein said polymeric film-forming agent is present in an amount of less than about 7.5% ~~(w/w), relative to~~ **of** the total weight of the composition.

76. The nail varnish of claim 47, wherein said polymeric film-forming agent is present in an amount of from about 8% to about 35% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

84. The nail varnish of claim 82, wherein said plasticizer is present in an amount of from about 0.1% to about 2% ~~(w/w), relative to~~ **of** the total weight of the composition.

85. The nail varnish of claim 82, wherein said plasticizer is present in an amount of from about 0.5% to about 10% ~~(w/w), based on~~ **of** the **total** weight of the non-volatile components.

90. The nail varnish of claim 47, wherein said volatile solvent is present in an amount of from about 60% to about 90% ~~(w/w), relative to~~ **of** the total weight of the composition.

93. A method of preparing a ~~sustained release~~ **prolonged effect therapeutic** varnish or spray formulation for treating the nail and surrounding tissues, comprising the steps of:

(f) preparing a solution, **said solution containing** ~~including~~ at least one volatile solvent;

(g) adding water to the solution prepared in (a);

(h) dissolving the pharmaceutically effective agents, and excipients in the solution prepared in (b);

(i) adding the humectant to the solution prepared in (c) when the formulation ingredients are completely dissolved; and

(j) dissolving the polymeric film forming agents in the solution prepared in (d)

said film-forming agents being selected so as to form a film upon evaporation of said volatile solvent, said film configured to trap water in contact with said nail and said surrounding tissues.